ELEVATED ARGININE VASOPRESSIN AND LOWERED ATRIAL NATRIURETIC FACTOR ASSOCIATED WITH HYPERTENSION IN COARCTATION OF THE AORTA

Impairment of humoral and neural regulation of blood pressure may contribute to preoperative and postoperative hypertension in coarctation of the aorta and may also affect the release of vasopressin and atrial natriuretic factor. Because vasopressin and atrial natriuretic factor have potent vasoactive effects, we measured plasma vasopressin and atrial natriuretic factor levels by radioimmunoassay before operation and for 5 days after operation in 11 patients aged 9 months to 12 years undergoing coarctation repair and in 12 control patients undergoing other cardiovascular operations. Six patients in the coarctation group required minimal antihypertensive therapy (group I) and five required prolonged intravenous antihypertensive therapy (group II). Before operation, vasopressin levels correlated with systolic blood pressure for all patients in the coarctation group ($r = 0.83, p < 0.01$) whereas atrial natriuretic factor levels did not. Before operation, atrial natriuretic factor levels were lower (28 ± 5 vs 41 ± 7 and 50 ± 8 pg/ml, $p < 0.05$) and vasopressin levels were higher (28 ± 6 vs 5.4 ± 0.9 and 7 ± 3 pg/ml, $p < 0.05$) in group II than in group I or control patients. Vasopressin levels were higher ($p < 0.05$) on the day of operation and on postoperative days 2 through 5 in group II than in group I and in control patients. Atrial natriuretic factor levels were lower during the day of operation in group II than in group I or in control patients (26 ± 7 vs 51 ± 16 and 50 ± 7 pg/ml, $p < 0.05$) and remained lower than control values on postoperative days 1 and 3 through 5. Elevated vasopressin and lowered atrial natriuretic factor levels may contribute to preoperative and postoperative hypertension in coarctation. (J THORAC CARDIOVASC SURG 1995;110:900-8)

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Coarctation of the aorta is commonly associated with hypertension, which is believed to be multifactorial in origin. Postulated causes include renovascular, humoral, vascular, and direct afterloading mechanisms.[1, 2] Persistent hypertension after repair of coarctation is also well described.[3] Explanations for postoperative hypertension include local vascular hyperplasia,[4] vascular hyperactivity,[5] changes in endothelium-dependent relaxation factor,[6, 7] and abnormalities of renal perfusion.[8] Alterations of baroreceptor,[9] sympathetic nervous system,[10] and renin-angiotensin system functions[11-14] have been demonstrated. These systems may also interact with atrial natriuretic factor (ANF) and vasopressin,[15, 16] and recent data suggest a role for these vasoactive hormones.[17-19] Because vasopressin and ANF have potent vasoactive effects and alterations in plasma levels could affect blood pressure in patients with coarctation, we studied the relationships among ANF, vasopressin, and blood pressure before and after repair of coarctation.

Methods

Eleven patients aged 9 months to 16 years (median 5.2 years) undergoing repair of coarctation had plasma vasopressin and plasma ANF levels measured before operation and at specific intervals after operation. Patients received a code number assigned by computer during

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processing of ANF and vasopressin samples to blind assays from clinical data. Before operation, no patients were maintained on medication regimens and no patients demonstrated findings of congestive heart failure. All patients underwent diagnostic catheterization of the left and right sides of the heart before operation, and hemodynamic data from those studies were used for correlation with preoperative vasopressin and ANF levels. All patients had preoperative systemic hypertension with respect to published age-matched standards[20, 21] and had left ventricular hypertrophy according to established electrocardiographic or echocardiographic criteria.[22, 23] The study was approved by the institutional review board at New York Medical College and informed consent was obtained for each patient.

Mean right atrial pressures were measured while indwelling lines were in place during the sampling period. Blood pressure in the right upper extremity was measured through radial arterial lines while those were in place and subsequently with a manometer cuff. Blood pressure in the lower extremities was measured with appropriately sized thigh cuffs. All patients had successful repair of coarctation with equalization of blood pressures in the upper and lower extremities after operation. No patients had strokes, ischemic bowel disease, or vertebral artery syndrome. Patients received medications after operation as needed to maintain blood pressure at or less than preoperative levels to maintain the integrity of the surgical site and to prevent postcoarctectomy syndrome. Intravenous nitroprusside was used in the early postoperative period; oral captopril was used afterward, by the second to third postoperative day. Patients who required less than 24 hours of intravenous nitroprusside to maintain blood pressure at or below preoperative levels were designated group I; patients who required more than 24 hours of this treatment were designated group II. Of the group I patients, four underwent patch graft repairs, one underwent subclavian flap repair, and one underwent a tube graft from the left subclavian artery to the descending aorta. Of the group II patients, three underwent patch graft repair, one patient underwent end-to-end resection, and one underwent a tube graft from the left subclavian artery to the descending aorta.

Twelve children undergoing other heart operations with cardiopulmonary bypass served as a control population. Diagnoses in the control group included atrial septal defect (two), ventricular septal defect (three), aortic stenosis (two), subaortic stenosis (one), pulmonary stenosis (two), and tetralogy of Fallot (two). Ages ranged from 0.8 to 16.0 years (median 5.7 years). No patients had symptomatic heart failure or abnormal blood pressure. Two patients had been receiving digoxin and furosemide before operation. Control patients had undergone diagnostic catheterization of the right and left sides of the heart before operation and had normal right and left atrial pressures. Coarctation and control groups received fentanyl during the induction of anesthesia and fentanyl plus halothane during operation.

ANF and vasopressin assays. Plasma ANF and vasopressin concentrations were measured before, during, and after operation at the following stages: (1) before operation, on admission to the hospital (preoperative), (2) during operation, after heart repair (intraoperative), (3) after operation, immediately on entry to the recovery room (RR1), (4) later on the day of operation while in the recovery area, an average of 6 hours after operation (RR2), (5) 1 day after operation (POD1), (6) on consecutive days after operation through postoperative day 5 (POD2, POD3, POD4, and POD5), and (7) in six of eight patients in the coarctation group who required nitroprusside therapy, blood samples were obtained immediately before and within 2 hours after the initiation of nitroprusside therapy. Blood samples between 2 and 3 ml in volume were taken for hormone assay. Preoperative samples were obtained by venipuncture on admission to the hospital for operation. During the first 48 hours after operation, blood was collected through an arterial line. Thereafter blood was collected by venipuncture. Each blood specimen was collected in a chilled vacuum container containing potassium ethylenediaminetetraacetic acid and 10 μl/ml blood aprotinin (17 TIU/ml; Ciba Pharmaceutical Co., Summit, N.J.). Blood samples were placed on ice immediately. Within 3 hours, tubes were spun briefly in a high-speed centrifuge; the serum was withdrawn with care to avoid the buffy coat, transferred to a second test tube, and frozen at −30° C to await extraction.

Hormone assays and extraction. Hormones were extracted with octadecyl-silane (Sep-Pak C18; Waters Chromatography Division, Millipore Corporation, Milford, Mass.) by means of a method previously reported:[24, 25] After thawing, plasma samples were acidified to pH 3 with 1% trifluoroacetic acid to which 8 ml 0.9% sodium chloride was added. The cartridge was consecutively activated with 8 ml 80% methanol, 10 ml air, 10 ml triethylamine acetate buffer at pH 4, and another 10 ml air. The diluted plasma was added and followed consecutively by 2 ml 9% sodium chloride, 8 ml double-distilled water, and 10 ml air. The elution of ANF and vasopressin was accomplished by passing 4 ml of a mixture of 1% trifluoroacetic acid and 80% methanol through the column at a rate of 1 drop/second. The eluate was lyophilized and reconstituted in buffer at a pH of 7.4.

ANF radioimmunoassay followed the method of Peninsula Laboratories Inc. (Belmont, Calif.) with minor modifications. Depending on a priori estimates of concentration, duplicate samples of 50, 100, or 150 μl plasma in polypropylene tubes were incubated for 16 hours at 4° C with 50 μl ANF antiserum (Peninsula Laboratories) diluted to a final volume of 350 μl. Iodinated tracer at 8500 counts/min was added and incubated for another 24 hours at 4° C. Separation of free and bound fractions was accomplished by adding 50 μl goat antirabbit gamma globulin and 50 μl normal rabbit serum, incubating for 2 hours at room temperature, and adding 1.0 ml ice-cold polyethylene glycol (30%). The final separation was achieved by centrifugation at 1300 *g* for 30 minutes at 4° C. The pellet was counted twice for 1 minute in a gamma counter. The ANF radioimmunoassay standard curve ranged from 0.5 to 128 pg/ml. Intraassay variability was 4%. Interassay variability was 8%. Percentage extraction has been measured with each previous assay per-

formed and has ranged consistently between 75% and 90%.[24]

Reconstituted samples for vasopressin radioimmunoassay used the method previously reported.[25] Samples for vasopressin were incubated for 24 hours with vasopressin-antibody complex (Behring Diagnostics Inc., Somerville, N.J.). Vasopressin labeled with iodine 125 (DuPont Diagnostic Imaging Division, North Billevica, Mass.) was added in a concentration of 8000 counts/min, incubated for 48 hours with the bound vasopressin-antibody complex, and then precipitated by the addition of polyethylene glycol as indicated for ANF. Tubes were spun in a refrigerated centrifuge at 1300 *g* for 30 minutes and radioactivity of the precipitated pellet was counted in a gamma counter. The vasopressin radioimmunoassay standard curve ranged from 2.5 to 100 pg/ml. Past intraassay variability was 4%. Interassay variability was 10%. Percentage extraction was measured with each previous assay performed and has ranged consistently between 90% and 95%.[25]

Statistical analysis. Means and standard errors of the mean were calculated and differences were determined by a two-way analysis of variance. Differences at $p < 0.05$ were required for statistical significance. Duncan's a posteriori test was used to determine intergroup differences.

Results

Group I comprised six patients and group II comprised five patients. Three of the six patients in group I required nitroprusside for less than 24 hours; the remaining three did not require any nitroprusside. One of the six patients in group I was discharged on a regimen of antihypertensive medication. All five patients in group II were discharged on regimens of oral antihypertensive medications. No relationships between ANF or vasopressin and mean right atrial pressure or preoperative mean pulmonary capillary wedge pressure could be established. For example, on postoperative days 1 through 4, right atrial pressure averaged 4 ± 1 mm Hg in group I and 5 ± 1 mm Hg in group II. No patients were left without oral intake for longer than any others. Fluid balance was not associated with changes in ANF or vasopressin levels. There was no relationship between type of coarctation repair and ANF or vasopressin levels.

ANF as a function of surgical stage. Fig. 1 and Table I present mean plasma ANF levels in patients undergoing repair of coarctation and control patients as a function of preoperative, intraoperative, and postoperative stage. Preoperative ANF levels and postoperative ANF levels during the first 24 hours after operation were significantly lower for patients in group II than for control patients. ANF levels were lower in patients in group II on postoperative days 3, 4, and 5 than in control patients. ANF levels were also lower in patients in group II on postoperative days 4 and 5 than in patients in group I.

Vasopressin as a function of surgical stage. Fig. 2 and Table I present mean plasma vasopressin levels in coarctation and control groups as a function of preoperative, intraoperative, and postoperative stage. Patients in group I had preoperative vasopressin levels comparable to control levels, whereas patients in group II had preoperative vasopressin levels markedly elevated with respect to control values. Vasopressin levels were highest during operation in control patients undergoing cardiopulmonary bypass and were also increased during operation in patients in both groups I and II. Vasopressin levels fell rapidly in patients in group I and in control patients, returning to preoperative levels by the second postoperative day. Vasopressin levels were significantly higher in group II than in control patients on entry to the recovery room and remained elevated on postoperative days 2 through 5. Vasopressin levels were also significantly higher in group II than in group I later on the day of operation and on postoperative days 2 through 5.

Blood pressure. Comparison of preoperative blood pressures and preoperative ANF levels showed no correlations in any patient group. There was, however, a significant correlation ($r = 0.83, p < 0.01$) between preoperative plasma vasopressin concentration and blood pressure (Fig. 3). Although patients in group II tended to have higher preoperative blood pressures, the difference between pressures in groups II and I was not significant (157 ± 7 mm Hg for group II, 134 ± 7 mm Hg for Group I). Postoperative blood pressures were medically controlled to maintain blood pressure at or lower than preoperative levels, as discussed previously. There were therefore no relationships between blood pressure per se and hormone levels in patients after operation.

Effects of nitroprusside. Nitroprusside was begun 3 ± 2 hours after arrival in the recovery room and was administered for 6 ± 4 hours in patients in group I who received the medication and 40 ± 15 hours in patients in group II. No patient received nitroprusside during postoperative days 3 through 5. To determine whether nitroprusside administration affected plasma ANF and vasopressin levels, we measured hormone levels im-

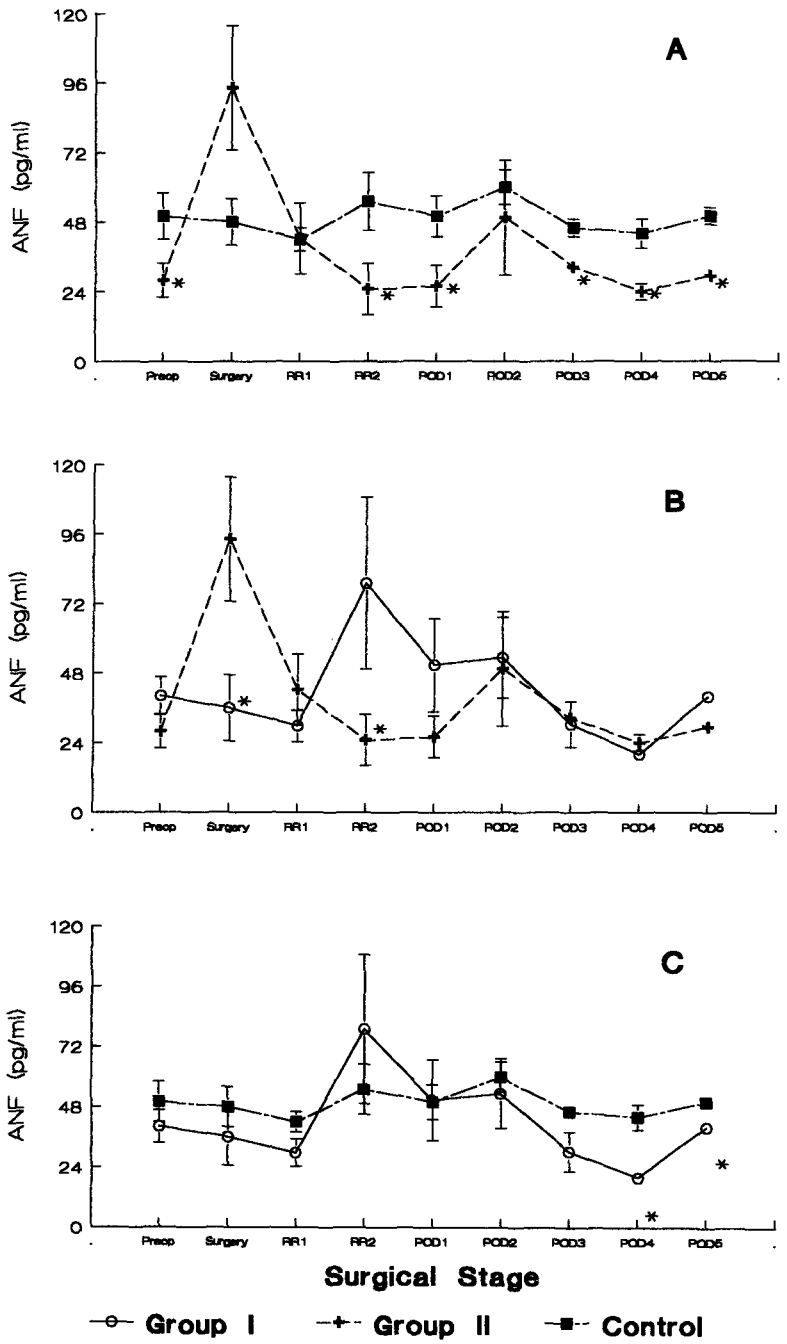

Fig. 1. Mean plasma ANF levels as a function of preoperative *(Preop)*, intraoperative *(Surgery)*, and postoperative stage are shown. **A,** Patients with coarctation who requiring prolonged intravenous nitroprusside (group II) versus control patients. **B,** Patients in group II versus patients in group I who did not require prolonged nitroprusside therapy. **C,** group I versus control patients. *Asterisks* represent significant difference at $p < 0.05$.

mediately before and within 2 hours after nitroprusside administration in six patients (four of the six patients in group II and two of the three patients in group I). Results are shown in Fig. 4. There was no significant change in vasopressin level related to nitroprusside. There was, however, a significant ($p < 0.05$) decrease in ANF level after nitroprusside administration.

Table I. *ANF and vasopressin in coarctation and control groups*

	ANF			*Vasopressin*		
	Group II	*Group I*	*Control*	*Group II*	*Group I*	*Control*
Preoperative	28 ± 6*	41 ± 7	50 ± 8	28 ± 6*	5.4 ± 0.9	7 ± 3
Intraoperative	94 ± 21	36 ± 11	48 ± 8	35 ± 11	49 ± 29	115 ± 10
RR1	42 ± 12	30 ± 5	42 ± 4	114 ± 26*	63 ± 15	60 ± 8
RR2	25 ± 9*	79 ± 30	55 ± 10	67 ± 15	32 ± 8	35 ± 4
POD1	26 ± 7*	51 ± 16	50 ± 7	31 ± 12	25 ± 14	15 ± 4
POD2	50 ± 20	53 ± 14	60 ± 6	30 ± 9*	8 ± 2	4 ± 2
POD3	33 ± 2*	30 ± 8	46 ± 3	19 ± 3*	9 ± 2	4 ± 1
POD4	24 ± 3*	20 ± 1	44 ± 5	21 ± 1*	9 ± 0.5	3 ± 2
POD5	30 ± 2*	40 ± 4	50 ± 3	18 ± 1*	10.5 ± 0.5	4 ± 2

*$p < 0.05$ compared with control.

Discussion

Vasopressin elevation in coarctation patients. Our data indicate that vasopressin levels were elevated before and after operation in patients with coarctation in group II who had postoperative hypertension for the longest time (Fig. 2). We have also shown that preoperative plasma vasopressin concentration was correlated with preoperative blood pressure in patients with coarctation (Fig. 3). Vasopressin may therefore contribute in part to preoperative and postoperative hypertension associated with coarctation of the aorta.

Absence of usual stimuli for vasopressin release. Stimuli for vasopressin release include hyperosmolarity and stimulation of cardiopulmonary mechanoreceptors.[26-29] Both low-pressure (e.g., atrial) and high-pressure (e.g., ventricular and aortic arch) receptors exist. Recent work suggests that high-pressure receptors may be more important for vasopressin release in primates and human beings.[30-32] Changes in calculated osmolarity did not occur in our patients. Hyperosmolality is thus unlikely to have been an important stimulus for vasopressin secretion in this series. Also, neither stimulation of high-pressure receptors by low systolic pressure nor stimulation of low-pressure receptors by low atrial pressures occurred in our patients. Patients with coarctation had normal atrial pressures and high blood pressures, which should have suppressed vasopressin release but did not. The usual regulation of vasopressin secretion was therefore absent in these patients.

Nonosmotic regulation of vasopressin depends on the sensitivity of cardiopulmonary mechanoreceptors as well as on their degree of stimulation. Previous work indicates that alterations in mechanoreceptor sensitivity do occur in coarctation. Blunted baroreceptor function has previously been reported both before and after surgical correction of coarctation.[9, 10, 33, 34] Abnormalities in high-pressure baroreceptor function are also consistent with our previously reported results,[25] in which neonates with left ventricular outflow tract obstruction, including some with coarctation, were studied. Alterations in baroreceptor function may have important effects on the release of vasopressin and, because vasopressin interacts strongly with baroreceptor regulation of blood pressure,[35] baroreceptor function may further influence blood pressure control in patients with coarctation. Abnormal vasopressin regulation could therefore be partially explained by altered baroreceptor function in patients with coarctation.

Decreased ANF in coarctation patients. Decreased ANF levels may also have a role in hypertension in our patients with coarctation. Our data indicate that preoperative and postoperative ANF levels during the first 24 hours after operation were significantly lower in patients in group II than in control patients or patients in group I. ANF levels in patients in group II were also lower than ANF levels in control patients during postoperative days 3 through 5. Low ANF levels in patients in group II early in the postoperative period may have resulted in part from decreased preload during nitroprusside administration. Nitroprusside was not given before operation or during postoperative days 3 through 5, and it therefore had no influence on low ANF levels at those times. Decreased ANF levels in patients with coarctation in group II who had sustained postoperative hypertension contrasts with previous studies, which showed that ANF levels were increased by hypertension.[36, 37] Also, elevated plasma vasopressin levels have been shown to increase plasma ANF levels.[38, 39] One would therefore expect ANF levels to be elevated in patients in group II with high vasopressin levels. Although a transient

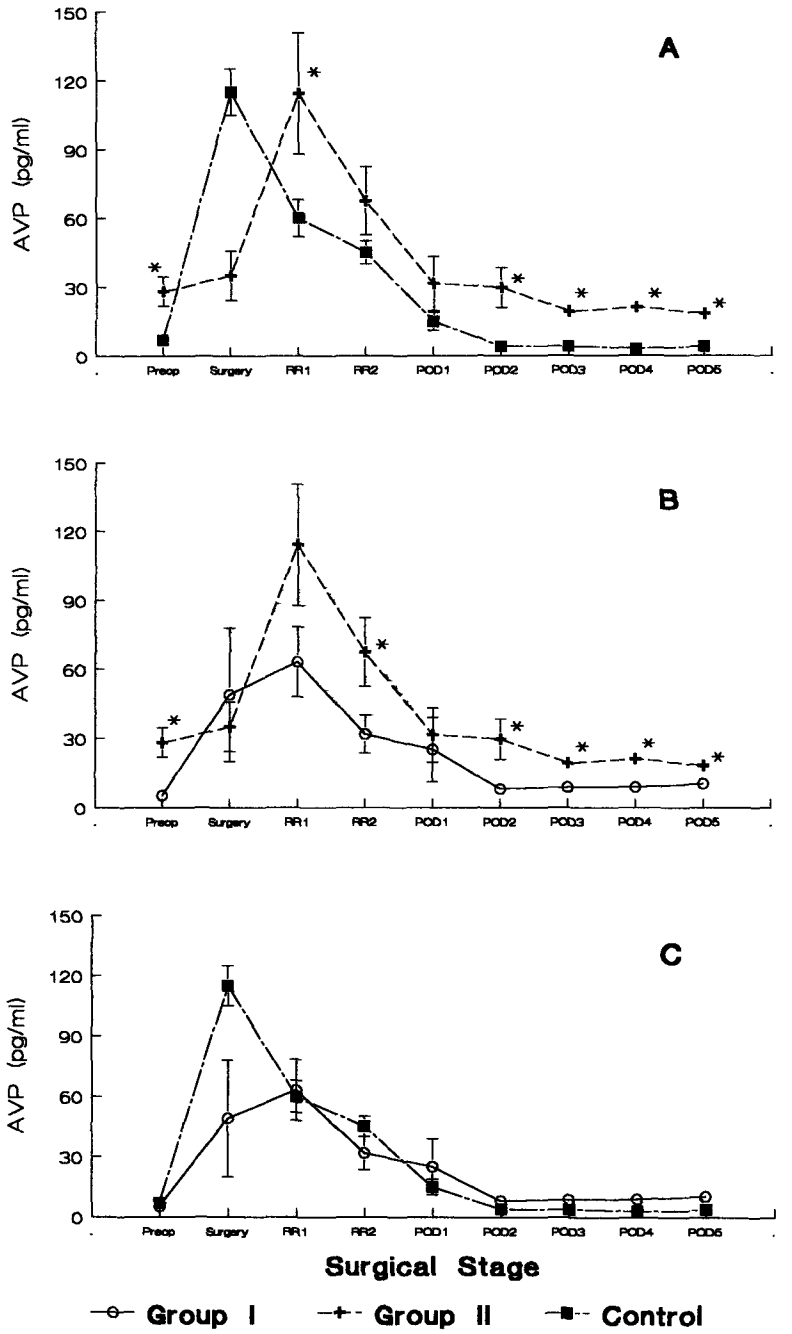

Fig. 2. Mean plasma vasopressin levels as a function of preoperative *(Preop)*, intraoperative *(Surgery)*, and postoperative stage are shown. **A,** patients with coarctation who required prolonged intravenous nitroprusside (group I) versus control patients. **B,** Patients in group II versus patients in group I who did not require sustained nitroprusside infusions. **C,** Group I versus control patients. *Asterisks* represent significant difference at $p < 0.05$.

perioperative rise in plasma ANF levels did occur in patients in group II, ANF levels returned rapidly to low preoperative levels. In patients with sustained postoperative hypertension, either an abnormality of ANF secretion or a depletion of ANF stores may be present. Low plasma ANF levels could potentiate hypertension through a withdrawal of ANF-induced vasorelaxation and its

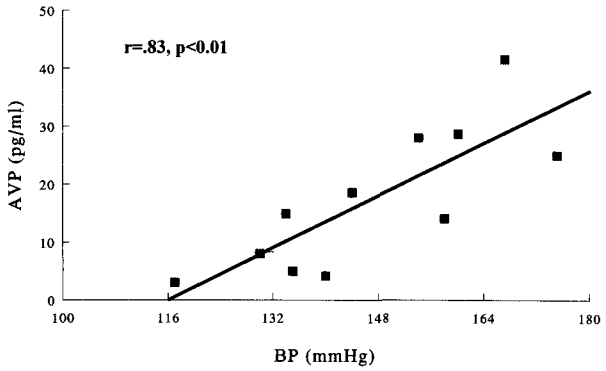

Fig. 3. The linear relationship between preoperative systolic blood pressure *(BP)* and plasma vasopressin level is shown for all patients with coarctation.

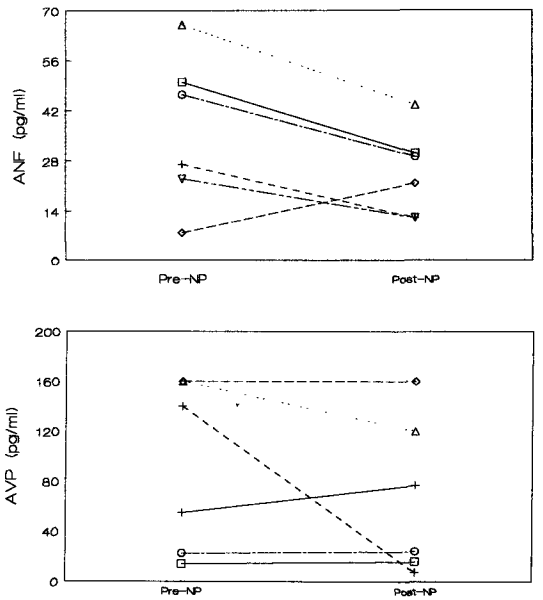

Fig. 4. Effects of nitroprusside. Plasma ANF levels *(top panel)* and vasopressin *(AVP)* levels *(bottom panel)* immediately before *(Pre-NP)* and 2 hours after *(Post-NP)* nitroprusside administration in six patients.

diuretic and natriuretic actions. Low ANF levels may also contribute to postoperative hypertension by decreasing ANF-induced inhibition of renin production, resulting in increased activity of the renin-angiotensin system as previously described in patients with coarctation.[11-14]

Decrease in ANF but not vasopressin with nitroprusside administration. Postoperative nitroprusside administration did not alter vasopressin levels but did decrease ANF levels further. This observation is consistent with our current understanding of the relation between ANF and atrial stretch[15]: as preload is decreased by nitroprusside, ANF release is inhibited by decreasing atrial stretch. Decreased blood pressure from nitroprusside administration normally would result in increased vasopressin levels. A lack of change in vasopressin level with nitroprusside administration may indicate a dissociation of already elevated vasopressin levels from usual arterial pressure regulation, as has been also been observed in patients with congestive heart failure.[40]

Operative and immediate postoperative vasopressin elevation. Transient operative and immediate postoperative elevations of vasopressin levels were observed in all patients and represent a nonspecific surgery-related increase in vasopressin level that has been reported previously.[41] As shown in that article, vasopressin release depends on the nature of surgery, with the highest plasma levels of vasopressin measured during cardiovascular surgery greater than during abdominal surgery, in turn greater than during superficial surgery. The surgical response is further increased by cardiopulmonary bypass[42, 43] as in our control group. Our control group is therefore a maximal control in the sense that it controls for the highest expected thoracic surgery–related vasopressin levels, as shown in Fig. 2. Nevertheless, except for patients with coarctation in group II vasopressin levels returned rapidly to normal levels within 24 hours after operation. The nonspecific response to surgery therefore cannot explain the differences observed among our subject groups. Rather, the data support the hypothesis that preoperative and postoperative hypertension in coarctation of the aorta may result in part from the pressor effects of vasopressin.

Similarly, all patients received opiates for anesthesia and analgesia, and it is known that opiates can affect vasopressin release. Naloxone in particular has been shown to suppress the nonspecific surge in vasopressin associated with surgery.[44] Fentanyl, on the other hand, exerts a permissive effect on vasopressin increase,[45] which is not significantly different from that of halothane alone.[44] All patients received similar postoperative morphine treatment for pain. As noted previously, however, except for patients with coarctation in group II, vasopressin levels returned rapidly to normal. An opiate response there-

fore cannot account for the differences measured between the groups.

Changes in the site of blood sampling, from venous before operation to arterial during the perioperative period to venous again after operation, may have affected measured ANF levels because plasma ANF levels are known to be somewhat higher in arterial than in venous blood in human beings.[46, 47] Nevertheless, differences in sampling site could not account for the differences in ANF levels between patients with coarctation in groups II and I or between patients in group II and control patients because blood samples were collected the same way for all.

Summary

In summary, our data indicate that elevated plasma vasopressin levels in the absence of an expected increase in plasma ANF levels occurs in patients with coarctation of the aorta. These hormonal changes may contribute to preoperative and to sustained postoperative hypertension observed in some patients with coarctation of the aorta.

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